TAIRE FAMILY KINASE INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application, U.S. Ser. No. 62/689,551, filed Jun. 25, 2018, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The members of the cyclin-dependent kinase (CDK) family play critical regulatory roles in proliferation. There are currently 20 known mammalian CDKs. Evidence shows that certain TAIRE family kinases including CDK14 (also known as PFTAIRE1 or PFTK1), as well as CDK15, CDK16, CDK17 and CDK18 play a role in cancer progression. Targeting TARE family kinases is therefore a promising therapeutic strategy in cancer. CDK14 has been implicated in promoting cell motility in cancer. For example, CDK14 has been implicated in promoting metastasis in various cancers, including, but not limited to, pancreatic cancer (Zheng, L., Zhou, Z. & He, Z. Knockdown of PFTK1 inhibits tumor cell proliferation, invasion and epithelial-to-mesenchymal transition in pancreatic cancer. *Int. J. Clin. Exp. Pathol.,* 8, 14005-12 (2015); hepatocellular carcinoma (Sun, T. et al., PFTK1 interacts with cyclin Y to activate non-canonical Wnt signaling in hepatocellular carcinoma. *Biochem. Biophys. Res. Commun.* 449, 163-8 (2014); and gastric cancer (Yang, L. et al. PFTK1 Promotes Gastric Cancer Progression by Regulating Proliferation, Migration and Invasion. *PLoS ONE,* 10, e0140451 (2015)). CDK14 has also been identified as contributing to neurological conditions or diseases, including gliosis (Duan C, et al., *J. Mol Neurosci.* 2015). Additional evidence suggests that certain TAIRE family kinases play a role in other cancers, and other diseases, including, but not limited to, metabolic disorders, and neurological diseases, and in male reproduction. CDK18 is implicated in diabetes, and CDK17 and CDK18 have been implicated in Alzheimer's disease, for which targeting these TARE kinases may be a promising therapeutic strategy (Potential role of PCTAIRE-2, PCTAIRE-3 and P-Histone H4 in amyloid precursor protein-dependent Alzheimer pathology. *Oncotarget.* 2016). CDK16 is implicated in several cancers, and is also implicated in spermatogenesis (Zi Z. et al., *pLoS Genet.* 2015). CDK15 is implicated in cancer apopotosis (ALS2CR7 (CDK15) attenuates TRAIL induced apoptosis by inducing phosphorylation of survivin Thr34. *Biochemical and Biophysical Research Communications.* 2014). The TAIRE family of cyclin-dependent kinases is comprised of CDK14, CDK15, CDK16, CDK17 and CDK18, all of which bind to Cyclin Y. (Mikolcevic, P. et al., *Cell Cycle,* 2012, 11 (20), 3758-68). Cyclin Y activates these kinases and is capable of targeting them to the plasma membrane. See id. These kinases are highly conserved but poorly characterized. Nonetheless the TAIRE family kinases are frequently overexpressed in a wide variety of cancers and associated with invasion, migration, and proliferation phenotypes. These oncogenic cell traits can be reduced by RNAi-induced knockdown of one or more of the TAIRE kinases, or Cyclin Y. (Yang, L. et al., *PloS One* 2015, 10 (10), e0140451; Liu, M. H.; et al., Knockdown of PFTK1 Expression by RNAi Inhibits the Proliferation and Invasion of Human Non-Small Lung Adenocarcinoma Cells. *Oncology Research* 2016, 24 (3), 181-7; Zhu, J.; et al., Knockdown of PFTAIRE Protein Kinase 1 (PFTK1) Inhibits Proliferation, Invasion, and EMT in Colon Cancer Cells. *Oncology Research* 2016, 24 (3), 137-44; Zheng, L.; et al., Knockdown of PFTK1 inhibits tumor cell proliferation, invasion and epithelial-to-mesenchymal transition in pancreatic cancer. *Int'l J. Clinical and Experimental Pathology* 2015, 8 (11), 14005-12; Zhang, W. et al., PFTK1 regulates cell proliferation, migration and invasion in epithelial ovarian cancer. *Int'l J. Biological Macromolecules* 2016, 85, 405-16; Zi, Z. et al., CCNYL1, but Not CCNY, Cooperates with CDK16 to Regulate Spermatogenesis in Mouse. *PLoS Genetics* 2015, 11 (8), e1005485).

[0003] CDK14 has been shown to regulate Wnt signaling during mitosis and is overexpressed in many Wnt-dependent cancers, such as colorectal and ovarian cancers. (Davidson, G. et al., Cell cycle control of wnt receptor activation. *Developmental Cell* 2009, 17 (6), 788-99; Zhou, Y. et al., Spontaneous genomic alterations in a chimeric model of colorectal cancer enable metastasis and guide effective combinatorial therapy. *PloS One* 2014, 9 (8), e105886. Ou-Yang, J. et al., Cyclin-Dependent Kinase 14 Promotes Cell Proliferation, Migration and Invasion in Ovarian Cancer by Inhibiting Wnt Signaling Pathway. *Gynecologic and Obstetric Investigation* 2017, 82 (3), 230-239). CDK16 is essential for spermatogenesis, and therefore, inhibitors of CDK16 may be developed as a form of male contraception. Mikolcevic, P.; et al., Cyclin-dependent kinase 16/PCTAIRE kinase 1 is activated by cyclin Y and is essential for spermatogenesis. *Molecular and Cellular Biology* 2012, 32 (4), 868-79; Zi, Z. et al., CCNYL1, but Not CCNY, Cooperates with CDK16 to Regulate Spermatogenesis in Mouse. *PLoS Genetics* 2015, 11 (8), e1005485). Due to the important regulatory functions of kinases, such as CDK's, including CDK14, CDK15, CDK16, CDK17, and CDK18, in cell cycle control, cell proliferation, differentiation, and apoptosis, it is important to develop modulators of the activities of these kinases, including selective modulators (e.g., selective inhibitors), for use as research tools as well as therapeutic agents in the treatment of various diseases and as agents for male contraception.

SUMMARY OF THE INVENTION

[0004] Described herein are compounds of Formula (I') or (I), and salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, and mixtures thereof. The compounds of Formula (I') or (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, may inhibit the activity of a kinase (e.g., a CDK) in a biological sample or subject. In certain embodiments, the kinase is a cyclin-dependent kinase (CDK). In certain embodiments, the CDK is CDK14. In certain embodiments, the CDK is CDK15, CDK16, CDK17, or CDK18. In certain embodiments, the compounds of Formula (I') and (I) are selective for CDK14 compared to other kinases. Described herein are methods of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, to study the inhibition of a kinase (e.g., CDK14, CDK15, CDK16, CDK17, CDK18) or as